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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Upon remand from the Board of Patent Appeals and Interferences, prosecution on the merits of this application is reopened on claims 1, 4-8, and 11 considered unpatentable for the reasons indicated below:

1. Claims 1, 4-8, and 11 are pending in the application and are currently subject to prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

3. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This ground of rejection is set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 7 in section (10)(A).

Applicant's arguments have been carefully considered but have not been found persuasive for the reasons set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 11 in section (11)(A).

Claim Rejections - 35 U.S.C. § 102

4. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Ditschuneit *et al.*, as evidenced by the disclosures of Pedreno *et al.* and Durrington *et al.*

This ground of rejection is set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 8 in section (10)(B).

Applicant's arguments have been carefully considered but have not been found persuasive for the reasons set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 21 in section (11)(B).

5. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Yoshino *et al.*

This ground of rejection is set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 9 in section (10)(C).

Applicant's arguments have been carefully considered but have not been found persuasive for the reasons set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 21 in section (11)(B).

6. Claims 1, 4-8, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Connor *et al.*

This ground of rejection is set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 9 in section (10)(D).

Applicant's arguments have been carefully considered but have not been found persuasive for the reasons set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 21 in section (11)(B).

7. Claims 1, 5, 6, and 11 are rejected under 35 U.S.C. § 102(b), as being anticipated by the disclosure of Kasiske *et al.*, as evidenced by the disclosures of Wyne *et al.*

This ground of rejection is set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 10 in section (10)(E).

Applicant's arguments have been carefully considered but have not been found persuasive for the reasons set forth in the Examiner's Answer mailed August 21, 2003, beginning at page 21 in section (11)(B).

Response to the Remand

8. In the remand, beginning at page 1, the Board of Patent Appeals and Interferences has requested clarification that the rejection over Kasiske *et al.*, as evidenced by the disclosures of Wyne *et al.*, includes only claims 1, 5, 6, and 11. The inclusion of claims 4, 7, and 8 in the rejection, as set forth in the Examiner's Answer mailed August 21, 2003 (page 21, section (11)(B)), was inadvertent. As indicated in the Final Office action mailed January 13, 2003, only claims 1, 5, 6, and 11 are rejected over Kasiske *et al.*, as evidenced by the disclosures of Wyne *et al.*

9. Beginning at page 2 of the remand, the Board of Patent Appeals and Interferences has commented upon the "written description" rejection. The Board of Patent Appeals and Interferences has stated that there appears to be a dispute as to how the claims should be interpreted. The Board of Patent Appeals and Interferences has suggested that Examiner revisit the issue of claim interpretation. Furthermore, the Board of Patent Appeals and Interferences has stated that the Examiner should address the reasons that the specification's disclosure that antisense nucleic acid molecules and ribozymes can be used to reduce the expression of apoE is not sufficient to meet the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

In response, the claims should be given the broadest reasonable interpretation that is both consistent with the supporting disclosure and consistent with that which would be understood by an artisan of skill in the relevant art. The claims are drawn to a method for reducing the plasma level of VLDL in a host, or of treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, said methods comprising administering to a host a member of a genus of agents that are capable of reducing the amount of plasma active apoE in a host by reducing "the expression of apoE".

On-Line Medical Dictionary (© Copyright 1997-2003 - The CancerWEB Project), which is available on the Internet at http://cancerweb.ncl.ac.uk/omd/index.html, indicates the term "expression" is a term of "molecular biology" and provides the following definition: "The process by which a gene's coded information is converted into the structures present and operating in the cell". The level of expression, and therefore the

expression of a gene, are provided or indicated by the measure of these structures (messenger RNA (mRNA) and protein) inside or outside the cell. Accordingly, the skilled artisan would appreciate that the process by which a gene's coded information is converted into structures present and operating in the cell, or for that matter, outside the cell, if the structure is secreted, or exported, is highly complex and notably, involves more than just transcription and translation. Moreover, the skilled artisan would appreciate that the process by which a gene's coded information is converted into structures present and operating in the cell, or for that matter, outside the cell, such as active plasma apoE, might involve transcription, mRNA processing and maturation, nuclear export, translation, post-translational processing, modification, and maturation, intracellular trafficking, and secretion or export. Therefore, given the broadest reasonable interpretation, the claims are drawn to a method for reducing the plasma level of VLDL in a host, or of treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, said methods comprising administering to a host a member of a genus of agents that are capable of reducing by whatever means the amount of plasma active apoE in a host.

As noted, for example, in the paragraph spanning pages 7 and 8 of the Examiner's Answer, the specification contemplates that the members of the genus of agents that may be found useable in practicing the claimed invention vary substantially in structure. The genus of structurally disparate agents includes, for example, small molecules, such as saccharides, fatty acids, steroids, purines, and pyrimidines, antibodies or binding fragments thereof, peptides, antisense nucleic acid molecules, and catalytic nucleic acids molecules, such as ribozymes.

Furthermore, despite commonly affecting the expression of apoE in a host, the members of the genus of agents to which the claims are directed have markedly different functions and therefore are capable of causing reductions in the expression of apoE by mechanisms or modes of operation that are vary markedly. For example, the mechanisms or modes of action by which an antibody and an antisense RNA molecule might cause a reduction in apoE expression differ. An antibody binds to an antigenic determinant on the surface of a molecule (e.g., a protein), whereas an antisense RNA molecule binds to a nucleic acid molecule (e.g., a mRNA molecule). An antibody that is

capable of reducing the expression of apoE will not bind directly to a mRNA molecule encoding apoE; and an antisense RNA molecule will not bind to a component of a ribosome to inhibit the translation of apoE. Furthermore, an antisense RNA molecule capable of inhibiting the expression of apoE is not necessarily an antisense RNA molecule that binds directly to a nucleic acid molecule encoding apoE, since it may bind to another nucleic acid molecule and inhibit its expression to thereby indirectly reduce the expression of apoE. Thus, the mechanisms or modes of operation by which these structurally and functionally disparate agents capable of reducing the expression of the gene encoding apoE are "direct" or "indirect" and often unrelated.

Consequently, given the broadest reasonable interpretation, the claims are directed to a genus of agents that differ both structurally and functionally, despite having the common ability to reduce the apparent expression of the gene encoding apoE in a host treated using the claimed invention, as measured by the level of plasma active apoE in the blood plasma of a host.

The structural and functional variability of the members of the genus of agents that are capable of reducing the amount of plasma active apoE, and therefore the apparent expression of the gene encoding apoE, is more evident upon consideration of the disparate structures and functions of the agents of the prior art having that capability. As noted, for example, in the paragraph spanning pages 19 and 20 of the Examiner's Answer, the prior art of record teaches four small molecules that differ markedly in structure, but which have been used to treat a disease condition associated with an elevated plasma level of very low density lipoproteins (VLDL) and/or to reduce the plasma level of VLDL in a host by a mechanism that involves reducing the level of apoE in the plasma of the host. As disparate are the chemical structures of these agents, the prior art of record, then, constitutes factual evidence that the skilled artisan would not have recognized that Applicant had possession of the claimed invention at the time the application was filed, because the specification fails to describe any *structural* feature that is commonly shared by the agents of the prior art, which might permit the skilled artisan to envision, recognize, or distinguish these and other members of the genus of agents to which the claims are directed.

In fact, the specification does not distinctly and specifically point out the identity of even one molecule or compound that is representative of the genus of agents that is suitable for use in practicing the claimed invention. Furthermore, the specification does not disclose any one particularly identifying structural feature that is common to at least a substantial number of the members of the genus that correlates with their common capability of reducing the expression of the gene encoding apoE. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language, generalized or otherwise, that describes compounds that achieve the claimed effect. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in practicing the claimed invention does not fulfill the written description requirement. Recognizing that the claims are drawn to a method comprising administering to a host an unspecified substance having the ability to reduce the expression of the gene encoding apoE, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to reduce the expression of the gene encoding apoE, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must

be capable of doing, not of the substance and structure of the members. In this instance, the supporting disclosure does not include the detailed structural and functional description of even one agent that is representative of the genus, as a whole, which can be used in practicing the claimed invention to reduce the expression of apoE in a host.

Although Lilly related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). The claimed method depends upon finding a compound that reduces the expression of apoE; without such a compound, it is impossible to practice the claimed methods.

In addition, although the skilled artisan could potentially identify agents that might be used in practicing the claimed invention by screening for substances that are capable of reducing the expression of apoE, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a substance that can be used as an agent for

reducing the expression of the gene encoding apoE in a host and that can be used treat a host suffering from a disease associated with the abnormal expression of the gene.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances capable of reducing the expression of apoE, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

The Board of Patent Appeals and Interferences has stated that the Examiner should address the particular reasons why the specification's disclosure of antisense nucleic acid molecules and ribozymes is not sufficient to meet the written description requirement, given that the nucleotide sequence of the gene encoding apoE was known at the time the application was filed. The claims are not drawn to a method comprising administering an antisense nucleic acid molecule or ribozyme that binds the mRNA encoding apoE to inhibit its translation. In point of fact, the claims are drawn to a method comprising administering an undisclosed substance that reduces the expression of apoE. Nonetheless, *were* the claims limited to a method comprising administering an antisense

RNA that binds to a mRNA encoding apoE and inhibits its translation, the supporting disclosure would still not provide adequate written description of the claimed invention.

Numerous reasons have already been set forth in the previous Office actions and the Examiner's Answer as to why the mere contemplation of antisense nucleic acids and ribozymes fails to evidence possession of the claimed invention at the time the application was filed. For example, at page 16 of the Examiner's Answer, it was noted that the Federal Circuit determined that antisense technology is highly unpredictable. See *Enzo Biochem Inc. v. Calgene Inc.,* 52 USPQ2d 1129 (CAFC 1999). As evidenced by the teachings of Sohail *et al.*, Pierce *et al.*, and Lesson-Wood *et al.*, antisense technology has still not yet advanced to the point of predictability. Guidelines (*supra*) states, "for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession" than would be required if the relevant art were mature (*Id.* at 1106). The structures of a representative or at least a substantial number of oligonucleotides that may be used to practice the claimed invention have not been disclosed, such that the skilled artisan could distinguish any such antisense nucleic acid molecule from others. Moreover, in view of the teachings of Sohail *et al.* and Pierce *et al.*, the disclosure of a non-limiting example of a target of an antisense oligonucleotide does not constitute a sufficient description of the genus of oligonucleotides to reasonably convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. From the teachings of the specification, the skilled artisan might be able to create a ribozyme, for example, albeit not without undue experimentation, that is capable of reducing the expression of apoE, which could be used in practicing the claimed invention; however, Applicant is again reminded that the written description requirement set forth under 35 U.S.C. § 112, first paragraph, is severable from the enablement requirement. Both requirements must be met by the supporting disclosure of the claimed invention. Furthermore, the written description provision requires more than the *ipsis verbis* appearance of the claim language; rather, it requires that the disclosure convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Moreover, the disclosure must

allow the skilled artisan to visualize or recognize the identity of the subject matter purportedly described. See *Enzo Biochem Inc. v. Gen-Probe Inc.,* 63 USPQ2d 1609 1616 (CAFC 2002).

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 30, 2005

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

L. HELMS, PH.D
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